Benzodiazepines and risk of all cause mortality in adults: cohort study

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ABSTRACT

OBJECTIVES

To evaluate the risk of all cause mortality associated with initiating compared with not initiating benzodiazepines in adults, and to address potential treatment barriers and confounding related to the use of a non-active comparator group.

DESIGN

Retrospective cohort study.

SETTING

Large de-identified US commercial healthcare database (Optum Clinformatics Datamart).

PARTICIPANTS

1:1 high dimensional propensity score matched cohort of benzodiazepine initiators, and randomly selected benzodiazepine non-initiators with a medical visit within 14 days of the start of benzodiazepine treatment (n=1252988), between July 2004 and December 2013. To address treatment barriers and confounding, patients were required to have filled one or more prescriptions for any medication in the 90 days and 91-180 days before the index date (ie, the date of starting benzodiazepine treatment for initiators and the date of the selected medical visit for benzodiazepine non-initiators) and the high dimensional propensity score was estimated on the basis of more than 300 covariates.

MAIN OUTCOME MEASURE

All cause mortality, determined by linkage with the Social Security Administration Death Master File.

RESULTS

Over a six month follow-up period, 5061 and 4691 deaths occurred among high dimensional propensity score matched benzodiazepine initiators versus non-initiators (9.3 v 9.4 events per 1000 person years; hazard ratio 1.00, 95% confidence interval 0.96 to 1.04). A 4% (95%

confidence interval 1% to 8%) to 9% (2% to 7%) increase in mortality risk was observed associated with the start of benzodiazepine treatment for follow-ups of 12 and 48 months and in subgroups of younger patients and patients initiating short acting agents. In secondary analyses comparing 1:1 high dimensional propensity score matched patients initiating benzodiazepines with an active comparator, ie, patients starting treatment with selective serotonin reuptake inhibitor antidepressants, benzodiazepine use was associated with a 9% (95% confidence interval 3% to 16%) increased risk.

CONCLUSIONS

This large population based cohort study suggests either no increase or at most a minor increase in risk of all cause mortality associated with benzodiazepine initiation. If a detrimental effect exists, it is likely to be much smaller than previously stated and to have uncertain clinical relevance. Residual confounding likely explains at least part of the small increase in mortality risk observed in selected analyses.

Introduction

Benzodiazepines are one of the most commonly prescribed classes of psychotropic drugs in developed countries.¹ In 2008, approximately 5.2% of US adults aged 18 to 80 years used benzodiazepines in an outpatient setting,² with use increasing from 4.1% in 1996 to 5.6% in 2013.³ Similarly, an estimated 8.4% of the population in British Columbia, Canada used a benzodiazepine in 2006, and 5.8% up to 16.3% used benzodiazepines across several European countries in 2008.⁴ Use seems to increase with age, with a higher proportion of any and long term use among patients aged more than 50 years.² Because of their established efficacy,⁵⁻⁷ benzodiazepines are widely used in the treatment of anxiety and sleep disorders,^{18 9} which together with mood disorders have been found to be the most common indications for a prescription for benzodiazepines by the US Medical Expenditure Panel Survey in 2013.³

Despite earlier mixed results about a possible association between benzodiazepines and all cause mortality,¹⁰ and mostly no indication of an increased risk among patients aged 65 years or older beyond falls and fractures related mortality,¹¹⁻¹⁴ more recent evidence has reported a threefold or higher increase in the risk of all cause mortality among adult populations using benzodiazepines,^{15 16} even for durations shorter than one month. Moreover, several studies conducted in adult or young adult populations have not provided support for a specific effect of benzodiazepines that could explain the increased risk in all cause mortality but have rather suggested associations with a wide range of causes of death, including cardiovascular disease,¹⁷⁻²⁰ cancer,^{15 18-21} respiratory disease,²⁰ and suicide.^{18 19 22}

WHAT IS ALREADY KNOWN ON THIS TOPIC

Because of their established efficacy for the treatment of anxiety and insomnia, benzodiazepines are one of the most commonly prescribed classes of psychotropic drugs in developed countries

Evidence has suggested a threefold or higher increase in the risk of all cause mortality among adults who use benzodiazepines, even for short durations Although these findings are supported by large studies yielding precise estimates in a few instances, several concerns remain, including a lack of specificity of the effect, unclear biological mechanism, and several potentially important study design limitations

WHAT THIS STUDY ADDS

This study found either no increase or at most a minor increase in all cause mortality risk associated with benzodiazepine initiation

If a detrimental effect exists, it is likely to be much smaller than previously reported and to have uncertain clinical relevance

Although these studies included large populations and yielded precise estimates in a few instances, several concerns remain, such as lack of specificity of the effect and strong associations across a spectrum of different outcomes, unclear biological mechanisms, and several potentially important study design limitations, including confounding and selection bias.

Given the large number of people who use benzodiazepines and the severity of the outcome, the posited strong associations between benzodiazepines and mortality have important public health implications. We therefore evaluated the risk of all cause mortality associated with use of benzodiazepines in a large commercial US health insurance database, mitigating the impact of confounding through specific study design and analytic strategies.

Methods

Sources of data

We collected data from Optum Clinformatics Datamart (OptumInsight, Eden Prairie, MN), a large US commercial insurance database covering more than 14 million people annually from all 50 US states. For each participant, the dataset contains demographic information, health plan enrollment status, inpatient and outpatient medical encounters (coded using the international classification of diseases, ninth revision, clinical modification, and current procedural terminology, fourth edition), and drugs filled on an outpatient basis, including the national drug code numbers, quantity dispensed, and days' supply. Data were available from January 2004 through December 2013.

Study population, medication use, and outcome definition

The exposed study population included patients aged 18 years and older who started a benzodiazepine (see eTable

1 in supplementary appendix for a list of benzodiazepines) between 1 July 2004 and 31 December 2013, and had six months of continuous health plan enrollment before drug initiation—that is, the index date for patients who start benzodiazepines (fig 1). We defined benzodiazepine initiators as those who had no use of any benzodiazepine in the previous six months. Patients were not allowed to enter the study cohort more than once. We opted for a primary non-active comparator group because the entire benzodiazepine class has been previously associated with an increased mortality risk, which precludes the use of a within class comparator, and because benzodiazepines have a wide range of indications and uses, which makes the selection of an appropriate out-of-class comparator group challenging. Non-users can have quite different characteristics from benzodiazepine initiators, such as a lower burden of comorbidities, and thus a lower mortality risk, or conversely higher barriers to treatment and surveillance for comorbidities, and thus a higher mortality risk²³; both scenarios will need to be accounted for through proper study design or analysis choices, or both. To select patients who did not start benzodiazepine treatment with similar opportunity to be evaluated and treated by a physician as patients who started benzodiazepines and within a similar time window, for each benzodiazepine user we identified a random patient who had a medical visit within 14 days either way of the treatment start date for the corresponding benzodiazepine user and fulfilled the same inclusion criteria as benzodiazepine new users—that is, six months of continuous health plan enrollment before the selected medical visit and no use of any benzodiazepine in the six months before and including the date of the visit (ie, the index date for patients who did not start benzodiazepines). We also required patients who either did or did not start benzodiazepines to have at least one filled prescription in the 90 days before the index date and at least one filled prescription in the previous 91 through 180 days, to balance surveillance between groups and to make sure that patients in both groups were in contact with the healthcare system and had equal treatment opportunity. Starting from the patients with the earliest date for starting benzodiazepines in the study period, we repeated these steps for each patient who started benzodiazepines throughout the study period until the last such patient was identified. For patients contributing to both cohorts of users and non-users of benzodiazepines, we only considered the first cohort entry (see supplementary appendix eFigure 1 for study diagram).

Follow-up began on the day after the index date for both cohorts. Patients were followed in an intention-to-treat approach until the occurrence of death, nursing home admission, end of continuous health plan enrollment, end of the study period (31 December 2013), or end of the observation period, whichever came first. Consistent with an intention-to-treat approach, we disregarded treatment variations occurring during the follow-up for both cohorts. We considered a six month observation period (180 days) in the main analysis and observation periods of 12 and 48 months of follow-up in sensitivity analyses. A 180 day observation period was chosen for the primary analysis as we empirically

Fig 1 | Flowchart of study cohort

observed that in routine care approximately two thirds of patients who start benzodiazepines stop treatment within the first two months.

The study outcome was all cause mortality identified by linkage of the Optum Clinformatics Datamart database with the Social Security Administration Death Master File.²⁴ The specificity of this master file for detecting mortality status has been estimated to range between 97% and 100%.^{25 26}

Characteristics of patients

Patient characteristics were identified during the six months preceding and including the index date and included demographic information (age, sex), calendar year, comorbidities and lifestyle factors, use of medications, and indicators of healthcare utilization. We purposely considered a large number of patient characteristics to capture both overt risk factors for mortality and variables that may be proxies of risk factors that were unmeasured or incompletely measured in our dataset. Supplementary appendix eTable 2 shows the complete list of patient characteristics.

Statistical analysis

We cross tabulated patient baseline characteristics by those who started or did not start benzodiazepines, and in both groups we calculated number of mortality events and incidence rates. Cox proportional hazards analyses were used to estimate hazard ratios with 95% confidence intervals for the association between benzodiazepines and all cause mortality. Results are presented for three levels of adjustment: unadjusted, adjusted using 1:1 propensity score matching, to control for measured confounders²⁷; and adjusted using 1:1 high dimensional propensity score matching, to further control for potential residual confounding.²⁸ Exposure propensity scores were derived from the predicted probability of benzodiazepine treatment estimated in a logistic regression model that contained all patient characteristics (see supplementary eTable 2) without additional variable selection. Groups were 1:1 matched on their propensity score using a nearest neighbour matching algorithm without replacement.²⁹ We calculated absolute standardized differences to assess covariate balance before and after propensity score matching.³⁰ Through the high dimensional propensity score algorithm, an automated technique that identifies and prioritizes covariates that may serve as proxies for unmeasured confounders in large electronic healthcare databases,²⁸ we selected a total of 200 empirically identified confounders and combined these with the investigator identified covariates (see supplementary appendix eTable 2) to estimate an empirically enriched propensity score. Stratification on the propensity score matched and high dimensional propensity score matched pair in Cox proportional hazards models to account for potential informative censoring did not change the point estimates appreciably, so this was omitted from all the adjusted analyses.

To test the robustness of our primary findings we performed subgroup and sensitivity analyses. Firstly, we

varied the definition of exposure risk window and extended the observation period to 12 and 48 months of follow-up. Secondly, as greater risks for outcomes associated with the hypnotic effects of benzodiazepines have been found among older patients³¹ and possibly among users of benzodiazepines with longer half lives,^{32 33} we tested the potential for effect modification of benzodiazepines on mortality according to age categories (<65 years and ≥65 years) and duration of action (short acting and long acting, ie, <24 hours half life and ≥24 hours half life) (see supplementary appendix eTable 3).³⁴ For these analyses, we estimated separate propensity scores for each subgroup. Thirdly, to address potential residual confounding associated with the use of a non-active comparator, we explored the use of an active comparator and performed analyses comparing initiators of benzodiazepines with initiators of selective serotonin reuptake inhibitor (SSRI) antidepressants for risk of all cause mortality. We chose SSRIs as the active comparator group because benzodiazepines and SSRIs are both psychotropic drugs and have some overlap in underlying indications, and because SSRIs have no known association with mortality, except for a possible association with increased suicidality in children and young adults.^{35 36}

All analyses were done using SAS 9.3 Statistical Software (SAS Institute, Cary, NC).

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Results

Study cohort and patient characteristics

Overall, 4 182 305 patients had filled a prescription for a benzodiazepine and 35 626 849 patients had a physician visit between July 2004 and December 2013 in the study database. After application of inclusion and exclusion criteria and random selection of comparison patients with a physician visit within 14 days either way of starting a benzodiazepine, our analytic sample included 1 686 410 patients who had started a benzodiazepine and 1 930 159 patients who had not but underwent a medical visit (fig 1). A total of 243 749 patients who had started benzodiazepines were excluded because they were selected as patients who had not started treatment before they started benzodiazepine. Short acting benzodiazepines were more frequently prescribed than long acting benzodiazepines, representing approximately 75% of filled prescriptions. Alprazolam was the most commonly prescribed agent among short acting benzodiazepines (47.2%), and diazepam was the most commonly prescribed agent among long acting benzodiazepines (87.7%).

Table 1 presents selected patient characteristics (see supplementary appendix eTable 2 for a complete list).

Table 1 | Selected baseline characteristics of study participants before and after high dimensional propensity score matching. Values are percentages unless stated otherwise

Characteristics	Before propensity score matching			After propensity score matching		
	Benzodiazepine initiators (n=1686 410)	Benzodiazepine non-initiators (n=1930 159)	Absolute standardized differences	Benzodiazepine initiators (n=1252 988)	Benzodiazepine non-initiators (n=1252 988)	Absolute standardized differences
Demographics:						
Mean (SD) age (years)	46.4 (13.8)	43.6 (14.6)	0.20	46.0 (13.8)	45.2 (14.6)	0.06
Men	534 592 (35.1)	770 133 (34.6)	0.17	439 799 (35.1)	433 534 (34.6)	0.01
Comorbidities and life style factors:						
Mean (SD) Charlson comorbidity score	0.5 (1.2)	0.4 (0.9)	0.18	0.5 (1.1)	0.4 (1.0)	0.01
Smoking	94 439 (5.6)	71 416 (3.7)	0.09	56 384 (4.5)	56 384 (4.5)	0.00
Obesity or overweight	77 575 (4.6)	75 276 (3.9)	0.03	53 878 (4.3)	52 625 (4.2)	0.00
Hypertension	468 822 (27.8)	424 635 (22)	0.13	320 765 (25.6)	325 777 (26)	0.01
Congestive heart failure	28 669 (1.7)	21 232 (1.1)	0.05	17 542 (1.4)	17 542 (1.4)	0.00
Ischemic heart disease	94 439 (5.6)	75 276 (3.9)	0.08	61 396 (4.9)	62 649 (5)	0.00
Cerebrovascular disease	32 042 (1.9)	21 232 (1.1)	0.07	13 783 (1.1)	13 783 (1.1)	0.00
Other cardiovascular diseases	102 871 (6.1)	79 137 (4.1)	0.09	63 902 (5.1)	63 902 (5.1)	0.00
Hyperlipidemia	441 839 (26.2)	426 565 (22.1)	0.10	310 741 (24.8)	315 753 (25.2)	0.01
Diabetes	163 582 (9.7)	171 784 (8.9)	0.03	120 287 (9.6)	121 540 (9.7)	0.00
Chronic obstructive pulmonary disease	55 652 (3.3)	36 673 (1.9)	0.09	32 578 (2.6)	31 325 (2.5)	0.01
Asthma	101 185 (6)	84 927 (4.4)	0.07	65 155 (5.2)	65 155 (5.2)	0.00
Pneumonia	32 042 (1.9)	25 092 (1.3)	0.05	20 048 (1.6)	20 048 (1.6)	0.00
Osteoarthritis	118 049 (7)	94 578 (4.9)	0.09	75 179 (6)	76 432 (6.1)	0.00
Other osteoarthritis and musculoskeletal disorders	489 059 (29)	440 076 (22.8)	0.14	324 524 (25.9)	324 524 (25.9)	0.00
Neuropathic pain	202 369 (12)	142 832 (7.4)	0.16	119 034 (9.5)	119 034 (9.5)	0.00
Back pain	382 815 (22.7)	285 664 (14.8)	0.20	233 056 (18.6)	233 056 (18.6)	0.00
Fractures	45 533 (2.7)	46 324 (2.4)	0.02	31 325 (2.5)	30 072 (2.4)	0.01
Falls	13 491 (0.8)	11 581 (0.6)	0.02	8771 (0.7)	8771 (0.7)	0.00
Kidney disease	57 338 (3.4)	46 324 (2.4)	0.06	36 337 (2.9)	36 337 (2.9)	0.00
Epilepsy or convulsions	25 296 (1.5)	15 441 (0.8)	0.07	13 783 (1.1)	12 530 (1)	0.01
Cancer	192 251 (11.4)	146 692 (7.6)	0.13	119 034 (9.5)	120 287 (9.6)	0.00
Anxiety	241 157 (14.3)	90 717 (4.7)	0.33	98 986 (7.9)	87 709 (7)	0.03
Insomnia	96 125 (5.7)	40 533 (2.1)	0.19	43 855 (3.5)	38 843 (3.1)	0.02
Other sleep disorders	89 380 (5.3)	65 625 (3.4)	0.09	55 131 (4.4)	52 625 (4.2)	0.01
Depression	274 885 (16.3)	154 413 (8)	0.26	144 094 (11.5)	139 082 (11.1)	0.01
Bipolar disorder	38 787 (2.3)	17 371 (0.9)	0.11	17 542 (1.4)	16 289 (1.3)	0.01
Psychosis	11 805 (0.7)	5790 (0.3)	0.06	5012 (0.4)	5012 (0.4)	0.00
Delirium	11 805 (0.7)	5790 (0.3)	0.06	6265 (0.5)	5012 (0.4)	0.01
Drug or alcohol misuse	37 101 (2.2)	23 162 (1.2)	0.08	20 048 (1.6)	18 795 (1.5)	0.01
Medications:						
ACE inhibitors	207 428 (12.3)	218 108 (11.3)	0.03	154 118 (12.3)	156 624 (12.5)	0.01
Angiotensin II receptor blockers	134 913 (8)	121 600 (6.3)	0.07	95 227 (7.6)	95 227 (7.6)	0.00
β blockers	237 784 (14.1)	202 667 (10.5)	0.11	162 888 (13)	161 635 (12.9)	0.00
Calcium channel blockers	145 031 (8.6)	202 667 (10.5)	0.06	101 492 (8.1)	105 251 (8.4)	0.01
Thiazide diuretics	82 634 (4.9)	77 206 (4)	0.04	57 637 (4.6)	62 649 (5)	0.02
Digoxin	11 805 (0.7)	9651 (0.5)	0.03	7518 (0.6)	7518 (0.6)	0.00
Anticoagulants	38 787 (2.3)	34 743 (1.8)	0.04	26 313 (2.1)	26 313 (2.1)	0.00
Antiplatelets	38 787 (2.3)	32 813 (1.7)	0.04	26 313 (2.1)	27 566 (2.2)	0.01
Non-insulin glucose lowering agents	119 735 (7.1)	133 181 (6.9)	0.01	88 962 (7.1)	97 733 (7.8)	0.03
Insulin	35 415 (2.1)	36 673 (1.9)	0.01	25 060 (2)	27 566 (2.2)	0.01
Lipid lowering agents	352 460 (20.9)	351 289 (18.2)	0.07	253 104 (20.2)	261 874 (20.9)	0.02
Oral corticosteroids	227 665 (13.5)	185 295 (9.6)	0.12	142 841 (11.4)	146 600 (11.7)	0.01
NSAIDs	298 495 (17.7)	287 594 (14.9)	0.08	199 225 (15.9)	214 261 (17.1)	0.03
Opioids	590 244 (35)	463 238 (24)	0.24	377 149 (30.1)	360 861 (28.8)	0.03
Anticonvulsants	148 404 (8.8)	81 067 (4.2)	0.19	76 432 (6.1)	73 926 (5.9)	0.01
SSRIs	377 756 (22.4)	223 898 (11.6)	0.29	239 321 (19.1)	189 201 (15.1)	0.11
Other hypnotics	195 624 (11.6)	82 997 (4.3)	0.27	100 239 (8)	76 432 (6.1)	0.07
Other anxiolytics	37 101 (2.2)	17 371 (0.9)	0.11	20 048 (1.6)	15 036 (1.2)	0.03
Antipsychotics	45 533 (2.7)	21 232 (1.1)	0.12	21 301 (1.7)	20 048 (1.6)	0.01
Barbiturates	38 787 (2.3)	21 232 (1.1)	0.09	22 554 (1.8)	17 542 (1.4)	0.03
Indicators of healthcare utilization:						
Any hospitalization	175 387 (10.4)	133 181 (6.9)	0.12	101 492 (8.1)	98 986 (7.9)	0.01
Mean (SD) No of hospital days	0.8 (4.2)	0.5 (3.1)	0.09	0.6 (3.4)	0.6 (3.6)	0.00
Mean (SD) No of physician visits	4.0 (3.6)	2.9 (2.9)	0.31	3.4 (3.2)	3.4 (3.1)	0.00
Mean (SD) No of prescription drugs	5.9 (4.0)	4.3 (3.1)	0.43	5.1 (3.6)	5.1 (3.4)	0.01
Psychiatric visit	382 815 (22.7)	210 387 (10.9)	0.32	199 225 (15.9)	182 936 (14.6)	0.04

ACE=angiotensin converting enzyme; NSAIDs=non-steroidal anti-inflammatory drugs; SSRIs=selective serotonin reuptake inhibitors.

We describe the covariates that are either more likely important risk factors for mortality or characterised by large imbalances (absolute standardized difference >0.1) between patients who initiated and did not initiate benzodiazepines. Compared with patients who did not initiate benzodiazepines, those who did were older, more often female, and had generally a higher burden of comorbidities, as measured by the Charlson comorbidity score.³⁷ Benzodiazepine initiators were more likely than non-initiators to have a history of hypertension, ischemic heart disease, heart failure, stroke, hyperlipidemia, diabetes, kidney disease, and cancer, and they were more often characterised by having painful conditions and psychiatric disorders, including anxiety, insomnia, depression, and drug or alcohol misuse. Benzodiazepine initiators were also more likely to use other hypnotic drugs, opioids, and antidepressants and to utilize healthcare more frequently. The prevalence of most characteristics, including the ones with small imbalances across exposure groups (absolute standardized difference <0.1) before adjustment for high dimensional propensity score, was consistently higher among benzodiazepine initiators than non-initiators. After propensity score matching, all patient characteristics between benzodiazepine initiators and non-initiators were well balanced (table 1), as assessed by absolute standardized differences <0.1.³⁰

In the primary analysis, the overall mean follow-up was 159 (SD 46) days for benzodiazepine initiators and 146 (56) days for non-initiators and the median was 180 days for both groups. Most patients were censored because of the end of the six month follow-up period (77.4% for benzodiazepine initiators and 65.7% for non-initiators), followed by the end of continuous health plan enrollment (18.6% and 30.4%, respectively).

Absolute and relative hazards

Overall, 8945 deaths occurred among benzodiazepine initiators (12.2 events per 1000 person years) and 5347 deaths among non-initiators (6.9 events per 1000 person years) within a six month observation period (table 2). Results from the unadjusted Cox regression analysis indicated that benzodiazepine initiators had a 79% increased risk of mortality compared with non-initiators (hazard ratio 1.79, 95% confidence interval 1.73 to 1.85). However, after 1:1 propensity score matching, the hazard ratio became consistent with no increased risk of death associated with benzodiazepine initiation compared with non-initiation (0.89, 0.85 to 0.93) and moved to 1.00 (0.96 to 1.04) in the 1:1 high dimensional propensity score matched population (table 2). High dimensional propensity score matched Kaplan-Meier

curves comparing the survival probability between benzodiazepine users and non-users were consistent with our findings (fig 2, upper panel).

Sensitivity and subgroup analyses

When we varied the definition for exposure risk window and extended the observation period to 12 and 48 months of follow-up, we identified a small statistically significant increased risk of mortality among benzodiazepine initiators compared with non-initiators (hazard ratio 1.04, 95% confidence interval 1.01 to 1.08 and 1.05, 1.02 to 1.07, respectively, table 3). The middle and lower panels in figure 2 display the Kaplan-Meier curves comparing the survival probability between the high dimensional propensity score matched benzodiazepine initiators versus non-initiators over 12 and 48 months of follow-up.

Stratified analyses by age and by benzodiazepine duration of action showed no increased risk of all cause mortality associated with benzodiazepine initiation among older patients or those initiating benzodiazepines with a longer half life (table 3). However, younger patients and patients using short acting benzodiazepines had a statistically significant, small increase in risk of all cause mortality compared with those who did not initiate benzodiazepines (1.09, 1.02 to 1.15 and 1.06, 1.02 to 1.10, respectively).

When SSRIs were used as the active comparator to benzodiazepines, results from the unadjusted Cox regression analysis indicated that benzodiazepine initiators had a 62% increased risk of mortality compared with non-initiators (1.61, 1.53 to 1.68). The hazard ratio moved to 1.09 (1.03 to 1.16) after 1:1 high dimensional propensity score matching (table 4).

Discussion

Using a propensity score matched and high dimensional propensity score matched cohort that included more than 2500 000 patients from a large commercial US health insurance database, we found no statistically significant difference in the occurrence of all cause mortality among patients who initiated benzodiazepines compared with non-initiators within a six month follow-up. We observed small, but statistically significant (owing to the large size of the cohort) increases in mortality risk associated with the initiation of benzodiazepines for follow-ups longer than six months, in younger patients, in patients initiating short acting drugs, and in the active comparison with selective serotonin reuptake inhibitor (SSRI) antidepressants. Although these results do not rule out the possibility of a small detrimental effect associated with benzodiazepines, this effect is

Table 2 | Risk of mortality associated with benzodiazepine initiation versus non-initiation in unadjusted, propensity score matched and high dimensional propensity score matched analyses within six months' follow-up

Analysis	Benzodiazepine initiators				Benzodiazepine non-initiators				Hazard ratio (95% CI)
	No of patients	No of events	Person years	Incidence/1000 person years	No of patients	No of events	Person years	Incidence/1000 person years	
Unadjusted	1 686 410	8945	733 918	12.2	1 930 159	5347	772 958	6.9	1.78 (1.73 to 1.85)
1:1 propensity score matched	1 256 630	4622	547 803	8.4	1 256 630	4839	503 208	9.6	0.89 (0.85 to 0.93)
1:1 high dimensional propensity score matched	1 252 988	5061	546 435	9.3	1 252 988	4691	500 932	9.4	1.00 (0.96 to 1.04)

Fig 2 | High dimensional propensity score matched Kaplan-Meier curves for survival probability since start of follow-up, and number of patients at risk

likely to be much lower than previously proposed.^{15 16} Moreover, the direction and extent of the attenuation of the point estimates with high dimensional propensity score adjustment in both the comparisons with benzodiazepine non-initiators and SSRI initiators, and the tight confidence intervals driven by the large size of our study, suggest that residual confounding—rather than a true effect of benzodiazepine drugs—could drive the

small increase in mortality risk observed in selected analyses.

Whether there is an effect on the risk of all cause mortality associated with the use of benzodiazepines has been an area of much discussion. The biological mechanism through which benzodiazepines would lead to an increased risk of all cause mortality is unclear. Benzodiazepines confer their effects through their action on γ -amino-butyric acid (GABA) type A receptors in the central nervous system, which are molecular substrates for the regulation of vigilance, anxiety, muscle tension, epileptogenic activity, and memory functions.³⁸ Because of their psychotropic action, benzodiazepines have been associated with hypnotic related side effects such as daytime sleepiness, impairment of psychomotor and cognitive functioning, increased risk of motor vehicle collisions, and increased risk of falls and fractures,³⁹⁻⁴² in particular among older patients,³¹ and with possible greater risks for benzodiazepines with a longer half life.^{32 33} Benzodiazepines have also been associated with an increased risk for development of dependence and misuse. However, this risk is not as substantial as with older sedatives and other recognised drugs of abuse,⁴³ and overdose with a benzodiazepine rarely causes severe cardiovascular or respiratory depression and death.³⁴ Yet several studies performed in adult populations have reported strong associations between benzodiazepines and all cause mortality, even for short durations of treatment,^{15 16 44} as well as associations with a wide range of causes of deaths, including cardiovascular disease¹⁷⁻²⁰ and cancer,^{15 18 19-22} for which the biological mechanism leading to an increased risk remains unclear. The lack of specificity of the effect identified in these investigations coexists with several potentially important limitations at the study design and analysis level, the most important being confounding.^{11 45 46} More specifically, it has been suggested that benzodiazepine treatment could be a “marker” for unmeasured underlying conditions resulting in death, rather than being the cause of death in itself.^{14 47} In support of this theory, several investigations have shown that health status and a history of multiple chronic conditions are independent predictors of benzodiazepine use.^{18 9} In line with this theory, we observed a consistently higher prevalence of mortality risk factors among benzodiazepine initiators compared with non-initiators or SSRI initiators, and large attenuations in the point estimates after high dimensional propensity score adjustment for both comparisons. The remaining small increase in risk is likely due to residual confounding. Residual confounding rather than true effect modification may also explain the moderate discrepancy in the risk of all cause mortality between patients aged less than and more than 65 years and between those using short acting and long acting benzodiazepines. In addition, the lack of an increased risk in all cause mortality among benzodiazepine initiators aged more than 65 years and among those initiators long acting agents further suggests that the hypnotic effects of benzodiazepines are likely not responsible for the increased risk observed in previous investigations.

Table 3 | Risk of mortality associated with benzodiazepine initiation versus non-initiation in high dimensional propensity score matched sensitivity and subgroup analyses

Analysis	Benzodiazepine initiators				Benzodiazepine non-initiators				Hazard ratio (95% CI)
	No of patients	No of Events	Person years	Incidence/1000 person years	No of patients	No of events	Person years	Incidence/1000 person years	
Follow-up duration (months):									
12	1 252 988	7671	986 396	7.8	1 252 988	6552	855 316	7.7	1.04 (1.01 to 1.08)
48	1 252 988	13 532	2 241 015	6.0	1 252 988	10 299	1 696 159	6.1	1.05 (1.02 to 1.07)
Patient age (years):									
<65	1 156 209	2160	504 932	4.3	1 156 209	1843	462 811	4.0	1.09 (1.02 to 1.15)
≥65	92 273	2599	39 716	65.4	92 273	2708	36 438	74.3	0.89 (0.85 to 0.94)
Drug duration of action:									
Short acting	1 011 732	4973	440 142	11.3	1 011 732	4370	403 954	10.8	1.06 (1.02 to 1.10)
Long acting	412 976	869	181 483	4.8	412 976	1341	165 450	8.1	0.60 (0.55 to 0.65)

Table 4 | Risk of mortality associated with benzodiazepine initiation versus selective serotonin reuptake inhibitors (SSRIs) initiation in unadjusted, propensity score and high dimensional propensity score matched analyses

Analysis	Benzodiazepine initiators				SSRI initiators				Hazard ratio (95% CI)
	No of patients	No of Events	Person years	Incidence/1000 person years	No of patients	No of events	Person years	Incidence/1000 person years	
Unadjusted	1 063 845	6008	465 228	12.9	649 400	2276	282 646	8.1	1.61 (1.53 to 1.68)
1:1 propensity score matched	563 088	2076	245 380	8.5	563 088	2096	245 252	8.5	0.99 (0.93 to 1.05)
1:1 high dimensional propensity score matched	549 022	2213	239 380	9.2	549 022	2032	239 261	8.5	1.09 (1.03 to 1.16)

Strengths and limitations of this study

Our study exhibits several strengths. In this large population based study, which included more than 1 250 000 high dimensional propensity score matched benzodiazepine initiators, we were able to evaluate the association between benzodiazepines and the risk of all cause mortality among adult patients as treated in a routine care setting. Through the use of a large, nationwide US commercial healthcare database (Optum Clinformatics Datamart), we had access to detailed patient information, including patient's diagnoses, use of medications, and measures of healthcare utilization. The linkage with the Social Security Administration Death Master File ensured that mortality was captured with high specificity, thus minimizing possible bias in the relative risk estimates. To minimize the potential for residual confounding, we employed multiple approaches in the study design and analysis, including the identification of benzodiazepine non-initiators who had similar patterns of healthcare utilization and treatment opportunity as benzodiazepine initiators, and the use of high dimensional propensity score analysis and an active comparator group to address potential unmeasured confounding. We also investigated the potential for effect modification in subgroup analyses by age and patients initiators benzodiazepines with shorter and longer half lives. The focus of the study on a middle aged, employed population, and the exclusion of frail participants who are not employed and not privately insured, may be one of the main advantages of this study as it is likely to control for a great deal of the confounding that may have been present in other studies.

Regardless, the main limitation to be considered remains confounding. Although the Optum Clinformatics Datamart database provides detailed patient information, certain relevant clinical information might not have been completely captured, because it is either not

fully or not directly measured in administrative data, and this may have led to residual confounding. We adjusted for confounding by comparing benzodiazepine initiators with non-initiators who had evidence of other medication use before cohort entry to reduce the risk of treatment barriers among non-initiators, and by using high dimensional propensity score methodology and an active comparator group to address potential unmeasured confounding through proxy identification. Despite these efforts, the potential for some residual confounding remains, which may have driven the positive associations observed in selected analyses.

Conclusions

Results from this large cohort study based on an intention-to-treat approach suggest either no increase or a small increase in the risk of all cause mortality associated with benzodiazepine initiation. If a detrimental effect on all cause mortality exists, it is likely to be much lower than previously stated and to have only modest clinical relevance, given its magnitude from both an absolute and a relative perspective. The direction and the extent of the attenuation in the point estimates with increasing levels of adjustment, suggest that residual confounding likely explains at least part of the small increase in mortality risk observed in selected analyses.

Contributors: EP and KFH were involved in all parts of the study. RL and MPL were involved in data analysis and revising the manuscript. RJG was involved in designing the study and revising the manuscript. All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. EP and KFH are the guarantors.

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Ethical approval: The use of this dataset for research was approved by the institutional review board (No 2013P000573) of the Brigham and Women's Hospital, Boston, MA and a data use agreement was in place.

Data sharing: No additional data available.

Transparency: The manuscript's guarantors (EP and KFH) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Supplementary material: eTables 1-3 and eFigure 1